Bench to Bedside Neuropharmacology Approaches to Treat Obesity: the Good, the Bad, and the Sick

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2008 USA Direct Medical Care Costs: $168 Billion (17% Total USA Med)
Obese individuals spend ~$2,800 more each year on health care

Cawley and Meyerhoefer, 2012
Hunger, Satiety, Nausea: Points on the Same Curve of Ingestive Behavior

Anti-Obesity Drugs Designed to Augment Endogenous Satiation Signals

Association Index

Positive

Negative

Time

Ingestion

Satiety

Satiation

Hunger

Satiety + Dessert

Fullness

Nausea

Malaise

Vomiting

5

4

3

2

1

0

-1

-2

-3

-4

-5

-1

-2

-3

-4

-5

-5

-4

-3

-2

-1

0

1

2

3

4

5
Control of food intake

“Meals are the fundamental unit of energy intake.” GP Smith

Appetite  Hunger

Meal Initiation

Feed forward POSITIVE response (“Reward”) to the presence of palatable food in the oral cavity

Time

Projected Rostrally

Nucleus Tractus Solitarius (NTS)
in medulla oblongata

Facial nerve (VII)

Glossopharyngeal nerve (IX)

Vagus Nerve (X)
The Gustatory System is postulated to be essential in distinguishing palatable (rewarding / energy rich) foods from non-palatable foods (energy poor / noxious).
Control of food intake

“Meals are the fundamental unit of energy intake.” GP Smith

Meal Initiation

Appetite

Hunger

Satiation Signals:
within-meal food intake
inhibitory signals

Satiation

(Meal Termination)

Satiety

Meal Initiation

Inter-meal-interval

Time
Sham feeding paradigm

Real Feeding

Sham Feeding


De Jonghe, et al 2005
Control of food intake

“Meals are the fundamental unit of energy intake.”

GP Smith

Satiation Signals:
within-meal food intake inhibitory signals

Appetite  Hunger

Meal Initiation

Satiation

(Meal Termination)

Satiety

Inter-meal-interval

Meal Initiation

Time
The Vagus Nerve – a conduit of communication between the brain and peripheral organs

Other Organs with Vagal Innervation:

- Kidney
- Gallbladder
- Adipose Tissue
- Esophagus
- Oral Cavity

Adapted from Silverthorn DU, et al.
Control of food intake

“Meals are the fundamental unit of energy intake.” GP Smith

Satiation Signals
- Gastric distension
- Cholecystokinin (CCK)
- Serotonin (5-HT)
- Glutamate
- Bombesin
- Peptide YY
- Enterostatin
- Glucagon-like Peptide 1 (GLP-1)
"These obesity studies have me worried... I'm going to drive next door for a checkup."

What about physical activity?
Food Intake is under CNS Control. What is the role of GLP-1?

Endogenous source of GLP-1 - preproglucagon

GLP-1R and/or GLP-1-binding
GLP-1 Receptor Agonists As a Pharmacological Treatment for Obesity?

Exendin-4 (Byetta)
- ~ Half-life of 2.5 hrs
- Delivered by SQ injection twice daily (b.i.d.)

Liraglutide (Victoza)
- ~ Half-life of 13 hrs
- Delivered by SQ injection once daily (q.d.)

FDA and EMA Approved Treatments for Type II Diabetes Mellitus – Incretin Effects Resistant to Degradation by Enzyme DPP-IV and Reduced Renal Excretion

• GLP-1 receptor ligands (e.g., exendin-4 and liraglutide) for obesity treatment:
  • Reduce food intake and body weight in humans and animal models
  • Negligible risk of life-threatening adverse events
    • Blonde et al, 2006; Pinkney et al, 2010; Montanya and Sesti, 2009; Buse et al, 2009
Food Intake and Body Weight Suppression Following Acute Intraperitoneal (IP) Administration of Liraglutide or Exendin-4

Hayes, Kanoski et al., 2011 Obesity
Once Daily Liraglutide or Twice Daily Exendin-4 Produces Comparable and Pronounced Suppressions in Food Intake and Body Weight in DIO Rats

Hayes, Kanoski et al., 2011 Obesity

Daily HF Diet Intake

Body Weight Loss

Days of Consecutive Treatment

Cumulative Change in Body Weight (g)

Days of Consecutive Treatment

24h HFS-Diet Intake (g)

Days of Consecutive Treatment

-60 -50 -40 -30 -20 -10 0 10 20 30

-60 -50 -40 -30 -20 -10 0 10 20 30

-60 -50 -40 -30 -20 -10 0 10 20 30

-60 -50 -40 -30 -20 -10 0 10 20 30

Saline
Exendin-4 (3µg/kg) - q.d.
Exendin-4 (3µg/kg) - b.i.d.
Liraglutide (25µg/kg)
Liraglutide (50µg/kg)
How do these effects compare to human data?

Is the rat a good model for invasive exploration of GLP-1 physiology?
2x-daily administration of Exendin-4 reduces body weight

Blonde L, et al. 2006
Once-daily administration of Liraglutide reduces body weight

Hunger, Satiety, Nausea:
Points on the Same Curve of Ingestive Behavior

Anti-Obesity Drugs
Designed to Augment Endogenous Satiation Signals

Hunger
Satiety
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Association Index
Positive
Negative

Ingestion
Satiation
Satiety + Dessert
Fullness
Nausea
Malaise
Vomiting

Time

-5 -4 -3 -2 -1 0 1 2 3 4 5
GLP-1 Receptor Agonists As a Pharmacological Treatment for Obesity:

Can they reduce food intake WITHOUT producing Nausea and Malaise?

• GLP-1 receptor ligands (e.g., exendin-4 and liraglutide) for obesity treatment:
  • Reduce food intake and body weight in humans and animal models
  • Negligible risk of life-threatening adverse events

• GLP-1R ligands are not devoid of side effects that negatively impact quality of life and produce treatment attrition.

• ~20-50% of T2DM patients prescribed GLP-1 medication experience nausea and/or vomiting
  • Discontinuation of drug treatment in ~6-10%
  • Reduced dose tolerance in another ~15%.

• ~21 – 25% of T2DM patients cannot take the drug effectively due to nausea / vomiting
Given the frequency of nausea / vomiting reported by patients prescribed GLP-1-based pharmaceuticals and that this adverse event is often reported but rarely investigated, a number of important questions and research needs arise.

1. Does acute and long-term suppression of intake by GLP-1 receptor ligands always occur in conjunction with nausea / malaise?

2. What is the mechanism by which GLP-1 receptor activation induces nausea?

3. Can we ameliorate the nausea produced by GLP-1 therapy but still have reduced food intake and glycemic responses by these exogenous drugs?

4. Are there potential GLP-1 receptor populations in the periphery or CNS that when activated suppress food intake and body weight WITHOUT producing nausea / malaise?
Saline
Exendin-4 (3.0µg/kg; b.i.d.)
Liraglutide (50µg/kg; q.d.)

Cumulative Body Weight Gain (g)

Daily Food Intake (Percent of Saline-Treated Rats)

Kanoski, Rupprecht, Fortin, De Jonghe, Hayes, 2012
Saline
Exendin-4 (3.0µg/kg; b.i.d.)
Liraglutide (50µg/kg; q.d.)

Cumulative Body Weight Gain (g)

Daily Food Intake (Percent of Saline-Treated Rats)
Pica

The ingestion of non-nutritive substances

Kaolin Clay (aluminum silicate)

• A well-established proxy for emesis and model for studying nausea in non-vomiting species
  Takeda et al, 1993; Yamamoto et al, 2002; Seeley et al, 2000; Andrews and Horn, 2006; De Jonghe and Horn, 2008

• Like emesis, kaolin ingestion appears to be a defensive response to ingested toxins or general visceral malaise

• Pica model enables the long-term analysis of visceral malaise / nausea
- GLP-1 receptor activation produces pica in the rat, indicative of nausea / malaise
- Pica following chronic liraglutide treatment only occurs on the first day of treatment, consistent with the profile of weight loss
- Chronic exendin-4 administration produces a linear increase in pica
The magnitude of Pica by chronic delivery of Exendin-4 is similar to that following administration of the chemotherapy agent, cisplatin.
What is the Mechanism?

Can we increase the weight loss?

Are there GLP-1 Receptor Populations in the Body that will Reduce Food Intake BUT NOT Cause Nausea?
What is the site of action for GLP-1 receptor ligands when given peripherally?

Endogenous source of GLP-1 - preproglucagon

GLP-1R and/or GLP-1-binding

Vagal Afferents

Nodose Ganglion

Vagal Efferents

FOOD

GLP-1

IP Injection of GLP-1R Agonist

Exendin-4 or Liraglutide

PVH
DMH
VMH
ARC

VTA

LHA

PNB
NTS
AP

NAc

What is the site of action for GLP-1 receptor ligands when given peripherally?
The Vagus Nerve - a conduit of communication between the brain and peripheral organs

Other Organs with Vagal Innervation:
- Kidney
- Gallbladder
- Adipose Tissue
- Esophagus
- Oral Cavity

Adapted from Silverthorn DU, et al.
Subdiaphragmatic vagal deafferentation (SDA):

Most selective technique to transect all subdiaphragmatic vagal afferent fibers

- Separation of afferent and efferent fibers as they enter/leave the medulla
- Transection of the afferent rootlets of the left cervical vagus and transection of the dorsal trunk (right cervical vagus)

(Smith and Norgren, Am. J. Physiol. 249:R638-641, 1985)

Slide Courtesy of Wolfgang Langhans
Peripheral exendin-4 and liraglutide suppress food intake by activating GLP-1R expressed on vagal afferents as well as direct CNS GLP-1R activation.

Vagal afferents are required to mediate intake suppression for LOW DOSES of exendin-4 and liraglutide, but NOT HIGH DOSES.

Kanoski, Fortin, Arnold, Grill, Hayes 2011 *Endocrinology*
3rd ICV Injection of GLP-1R Antagonist [Exendin-(9-39)]

IP Injection of GLP-1R Agonist
Exendin-4 or Liraglutide

Endogenous source of GLP-1

GLP-1R and/or GLP-1-binding

Vagal Afferents

Vagal Efferents

FOOD

GLP-1
Peripheral exendin-4 and liraglutide suppress food intake by activating GLP-1R expressed on vagal afferents as well as direct CNS GLP-1R activation

Kanoski et al., 2011 Endocrinology

Blockade of central GLP-1R with the antagonist Exendin-(9-39) attenuates but does not reverse the intake suppression of peripheral GLP-1R agonists
Peripheral exendin-4 and liraglutide suppress food intake by activating GLP-1R expressed on vagal afferents as well as direct CNS GLP-1R activation.

Exendin-4 or Liraglutide

IP Injection of GLP-1R Agonist

Endogenous source of GLP-1: preproglucagon

GLP-1R and/or GLP-1-binding
The CNS GLP-1 system is physiologically involved in energy balance regulation.

PVH  DMH  VMH  ARC  PBN  NTS  AP  NAc  VTA  LHA

Endogenous source of GLP-1 - preproglucagon

What are the relevant GLP-1 receptor-expressing nuclei within the brain for energy balance control?
Human Obesity is Clearly **NOT** Driven by Metabolic Need Alone

Is it possible that the Reward System / Hedonic Nuclei of the Brain Could be Responsible for Human Obesity?
The excessive food intake that contributes to human obesity is clearly not driven by metabolic need alone.

It is critical to examine and better define the neural basis of non-homeostatic controls of food intake.

Would the GLP-1 system regulate food intake by modulating the rewarding value of food?

Modified from Narayanan et al. 2010
Do caudal NTS Proglucagon (GLP-1 producing) Neurons Project to the Mesolimbic Reward System?

Fluorogold = monosynaptic retrograde tracer

GLP-1R and/or GLP-1-binding

Endogenous source of GLP-1 - preproglucagon

Do caudal NTS Proglucagon (GLP-1 producing) Neurons Project to the Mesolimbic Reward System?

Alhadeff, Rupprecht and Hayes, 2012, *Endocrinology*
What is the role of VTA GLP-1Rs in food intake control?

- Determine whether intraparenchymal delivery of the GLP-1R agonist Exendin-4 into the VTA reduces food intake.
  - Examine food intake of various foods (sucrose, high-fat diet, standard chow).

Exendin-4 = GLP-1R agonist

GLP-1R and/or GLP-1-binding

Endogenous source of GLP-1 - preproglucagon
VTA GLP-1R Activation Dose-Dependently Reduces Palatable Food Intake and Body Weight

Intake of Preferred Liquid Food: 15% Sucrose

Intake of Preferred Solid Food: HF Diet (60% Kcal from fat)

Intake of Standard Rat Chow

* = p<0.05 from aCSF

Alhadeff, Rupprecht and Hayes, 2012, Endocrinology
What is the role of NAc core and NAc shell GLP-1Rs in food intake control?

- Determine whether intraparenchymal delivery of the GLP-1R agonist Exendin-4 into either the NAc core or shell reduces food intake.
  - Examine food intake of various foods (sucrose, high-fat diet, standard chow).
GLP-1R Activation in the NAc Core Reduces Palatable Food Intake and Body Weight

Intake of Preferred Liquid Food: 15% Sucrose

Intake of Preferred Solid Food: HF Diet (60% Kcal from fat)

Intake of Standard Rat Chow

* = p<0.05 from aCSF

Alhadeff, Rupprecht and Hayes, 2012, Endocrinology
GLP-1R Activation in the NAc Shell Reduces Body Weight and Intake of HF-Diet

Intake of Preferred Liquid Food: 15% Sucrose

![Graph showing cumulative sucrose intake over time with legend](image)

Intake of Preferred Solid Food: HF Diet (60% Kcal from fat)

![Graph showing cumulative HF diet intake over time with legend](image)

Daily Body Weight Gain

![Graph showing 24h BW change with legend](image)

Intake of Standard Rat Chow

![Graph showing cumulative chow intake over time with legend](image)

* = p<0.05 from aCSF

Alhadeff, Rupprecht and Hayes, 2012, *Endocrinology*
Are the NTS-to-MRS GLP-1 Projections Physiologically Relevant for the Normal Control of Food Intake?

Will Blockade of GLP-1R in the VTA and/or NAc Result in an Increase in Food Intake?
Endogenous GLP-1R Signaling in the VTA and NAc Core are physiologically involved in the control of food intake.

Alhadeff, Rupprecht and Hayes, 2011, Endocrinology
GLP-1R activation in the mesolimbic reward system does **NOT** produce nausea/malaise

**Pica:** The ingestion of non-nutritive substances

**Kaolin Clay** (aluminum silicate)

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**VTA**

24h Kaolin Intake

- aCSF
- exendin-4 (0.05µg)

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**NAc Core**

24h Kaolin Intake

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**NAc Shell**

24h Kaolin Intake

- Saline
- Cisplatin (6mg/kg; IP)
GLP-1R agonists Exendin-4 and Liraglutide reduce food intake and body weight by activating vagal afferent GLP-1R and also through direct activation of central GLP-1R.

NTS Proglucagon (GLP-1 producing) neurons project to nuclei in the Mesolimbic Reward System
- VTA, NAc core, and NAc shell

These NTS - to - MRS GLP-1 projections appear to be physiologically relevant for the control of feeding, as blockade of endogenous GLP-1R signaling in the VTA and NAc core increased HF diet intake

Exogenous activation of GLP-1R in either the VTA or the NAc dose-dependently reduces body weight and food intake of palatable foods.

Working Hypothesis: GLP-1 signaling reduces food intake, in part, by activating the Mesolimbic Reward System to reduce the rewarding value of food
GLP-1R and/or GLP-1-binding

Endogenous source of GLP-1 - preproglucagon

Vagal Efferents

Vagal Afferents

PVH
DMH
VMH
ARC

PBN
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Nodose Ganglion

GLP-1

FOOD

Exendin-4 or Liraglutide

IP Injection of GLP-1R Agonist
Injection of GLP-1R Agonist
Exendin-4 or Liraglutide

Endogenous source of GLP-1 - preproglucagon

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Exendin-4 or Liraglutide

Endogenous source of GLP-1 - preproglucagon

GLP-1R and/or GLP-1-binding

GLP-1R and/or GLP-1-binding
ACKNOWLEDGEMENTS

Hayes Lab:
• Elizabeth Baase
• Amber Alhadeff
• Laura Rupprecht
• Derek Zimmer
• Diana Olivios
• Research and Undergraduate Assistants

Collaborators:
• Harvey Grill, Penn
• Kendra Bence, Penn
• Scott Kanoski, Penn
• Wolfgang Langhans, ETH Zurich
• Myrtha Arnold, ETH Zurich
• Bart De Jonghe, Penn
• Samantha Fortin, Penn

Work Supported by:
NIH: DK085435 and DK093874 (M.R.H.)
Diabetes Research Center Pilot and Feasibility Grant
IISP from Merck & Co., Inc. (M.R.H. and H.J.G.)
Research Grant from Novo Nordisk (H.J.G. and M.R.H.)
University of Pennsylvania Research Foundation
Dept. of Psychiatry, Perelman School of Medicine at The University of Pennsylvania